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DOCKET NO.: GLIS- 0128 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Buhr, Et Al. **Confirmation No.: 4009**

Serial No.: 09/408,396 **Group Art Unit: 1623**

Filing Date: September 29, 1999 **Examiner: Howard V. Owens Jr.**

For: Nucleoside 5'-Methylene Phosphonates

DATE OF DEPOSIT: March 3, 2003

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TYPED NAME: Joseph Lucci
REGISTRATION NO.: 33,307
Leslie E. Aberman
REGISTRATION No.: Limited Recognition Under 37 CFR §10.9(b) attached

Assistant Commissioner for Patents
Washington DC 20231

Sir:

APPELLANT'S BRIEF PURSUANT TO 37 C.F.R. § 1.192

Applicants appeal the Final Rejection dated July 30, 2002 in connection with the above-identified application.

1. REAL PARTY IN INTEREST

Based on information supplied by Applicants and to the best of undersigned's knowledge, the real party in interest in the above-identified patent application is ISIS Pharmaceuticals, Inc., a corporation of Delaware, which is the assignee of Chris Buhr, Mark Matteucci, Norbet W. Bischofberger, and Brian Froehler.

2. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to Appellants, Appellant's legal representative, or the assignee which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending Appeal.

3. STATUS OF CLAIMS

Claims 1-26 are pending in the present application. Claims 1-8 have been indicated as containing allowable subject matter. Claims 9-26 are the subject of this Appeal. Claims 1-26 appear in Appendix A.

4. SUMMARY OF INVENTION

The present invention is directed to novel methylene phosphonate nucleosides which exhibit antiviral and antitumor activity and novel oligonucleotides derived from methylene phosphonate nucleoside monomers that have enhanced nuclease stability.

5. ISSUES

Two issues remain for resolution in this appeal:

1. Whether or not the Examiner has demonstrated that the subject matter of claims 9-19 would have been obvious to those of ordinary skill in the art in view of the respective disclosures of Gait, *Oligonucleotide Synthesis: A practical approach*, October 1984, Montgomery *et al., J. Medicinal Chem.*, 29, 2389-2392 (1986), Perlman *et al., J. Med. Chem.*, 28, 741-748 (1985), and Greene *et al., Protective Groups in Organic Chemistry*, pp. 413-416 (1991); and

2. Whether or not the Examiner has demonstrated that the subject matter of claims 20-26 would have been obvious to those of ordinary skill in the art in view of Gait, *Oligonucleotide Synthesis: A practical approach*, October 1984 and Sterzycki *et al.*, European Patent Application No. EP 0316017.

6. GROUPING OF CLAIMS

Applicants believe that claims 9-19 stand or fall together and that claims 20-26 stand or fall together.

7. ARGUMENT

1. The Rejection Of Claims 9-19 under 35 U.S.C. § 103 Is Improper.

There is no evidence of record indicating that those of ordinary skill would have been motivated to combine the teachings of the cited references in the manner the Examiner proposes. Given this lack of evidentiary support, the rejection of claims 9-19 for alleged obviousness is improper and should be withdrawn.

Claims cannot be found obvious in view of a combination of references unless the prior art itself suggests the desirability of the combination. *Berghauser v. Dann,* 204 U.S.P.Q. 393 (D.D.C. 1979); *ACS Hospital Systems Inc., v. Montefiore Hospital,* 221 U.S.P.Q. 929 (Fed. Cir. 1984). There must be something in the prior art that would have motivated persons of ordinary skill to make the combination. *In re Stencel,* 4 U.S.P.Q.2d 1071 (Fed. Cir. 1987), *accord, Ex parte Marinaccio*, 10 U.S.P.Q.2d 1716 (Pat. Off. Bd. App. 1989)(combining references is improper absent some teaching, suggestion, or motivation for the combination in the prior art).

Obviousness cannot be established by merely showing that it would have been possible for a person of ordinary skill to combine certain references. There must be affirmative evidence that such a person would have been "impelled" to make the combination. *Ex parte Levengood*, 28 U.S.P.Q.3d 1300, 1302 (Pat. Off. Bd. App. 1993)(citations omitted).

Here, there is no such affirmative evidence. Although the Examiner makes unsupported allegations that persons of ordinary skill would have been motivated to combine the respective teachings of the Gait, Greene, Perlman, and Montgomery references for the purpose of creating a protected 2-deoxy-2-fluoro-β-D-arabinofuranosyl compound, the Examiner has failed to provide any reason why such persons would have been motivated to make this combination in view of the teachings of the cited references. Both the Perlman and Montgomery references disclose unprotected compounds and the Examiner points to nothing in the references suggesting that their disclosed compounds would benefit from the use of protecting groups. Similarly, the Office Action fails to identify any discussion in the Greene or Gait references suggesting that the unprotected compounds disclosed in the Perlman and Montgomery references would benefit from the addition of protecting groups. As taught in the Gait reference, oligonucleotide synthesis requires a careful consideration of the structure of the oligonucleotide to be synthesized. Different strategies must be used depending upon the oligonucleotide to be synthesized. Accordingly, even though the Gait or Greene reference may generally suggest the use of protecting groups for the protection of exocyclic amino groups, it *does not* suggest the use of protecting groups for the particular compounds of the present invention. Nor do the Perlman or Montgomery reference suggest that a protecting group is necessary or desirable for the particular compounds of the present invention. There is simply no evidence that the skilled practitioner would not have been

motivated to use the protecting groups disclosed in the Gait reference or Green reference with the compounds disclosed in the Perlman or Montgomery references. Accordingly, the rejection of claims 9-19 for alleged obviousness should be withdrawn.

2. The Rejection Of Claims 20-26 under 35 U.S.C. § 103 Is Improper.

There is no evidence of record indicating that those of ordinary skill would have been motivated to combine the teachings of the cited references in the manner that the Examiner proposes, much less that such a combination would have produced a claimed invention. In fact, there is good reason to believe that those of ordinary skill in the art would not have been motivated to make this combination. Accordingly, the rejection of claims 20-26 for alleged obviousness is improper and should be withdrawn.

As best understood from the final Office Action, it is the Examiner's position that it would have been obvious to prepare oligonucleotides from the 2'-deoxy-2'-fluoro-arabinonucleosides disclosed by the Sterzycki reference, according to methods taught in the Gait reference. Applicants note, however, that the Office Action points to nothing in either reference that teaches or suggests the preparation of oligonucleotides from 2'-deoxy-2'-fluoro-arabinonucleosides. The Examiner's statement that general methods for preparing oligonucleotides are well known in the art falls short of providing motivation for making an oligonucleotide from the nucleosides disclosed in the Sterzycki reference – particularly when the Sterzycki reference teaches that its disclosed nucleosides find utility when they exist as monomers, and are ***not*** incorporated into an oligomer (*see, e.g.,* abstract on cover page).

It appears from the Action that perhaps the Examiner is basing his rejection on a motivation to make the inventions provided in Applicants' disclosure. Applicants teach on page 4 of the specification that oligonucleotides containing 2'-deoxy-2'-fluoro-

arabinonucleosides are of interest because the conformation of the sugar closely resembles that of RNA and consequently oligonucleotides containing 2'-deoxy-2'-fluoro-arabinonucleosides have a higher affinity to DNA than normal oligodeoxyribonucleotides. This recognition, however, is associated with the present invention and, therefore, would not have been available to one of ordinary skill in the art. As will be noted, "the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure, MPEP 2143, *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

In summary, there is no evidence of record indicating that those of ordinary skill in the art would have been motivated to modify the teachings of the prior art in any way that would have produced a claimed compound. Accordingly, the rejection of claims 20-26 under 35 U.S.C. § 103 should be withdrawn.

8. CONCLUSION

For the foregoing reasons, Applicants request that this patent application be remanded to the Examiner with an instruction to both withdraw the outstanding rejections and allow the appealed claims.

Date: March 3, 2003

Joseph Lucci
Registration No.: 33,307
Leslie E. Aberman
Registration No.: Limited
Recognition Under 37 CFR §10.9(b)
attached

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

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Assistant Commissioner for Patents,
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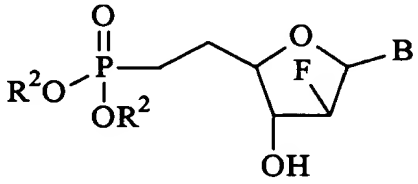
APPENDIX A TO APPELLANTS' BRIEF

1. A compound having the formula:



wherein:

B is adenosine, N^6-benzoyladenine, thymine, guanine, or N^2-isobutyrylguanine; and each R^2 is independently hydrogen, phenyl, alkyl (1-12C) or hydrogentriethylammonium ion.

2. The compound of claim 1 wherein B is guanine.

3. The compound of claim 2 wherein R^2 is hydrogen.

4. The compound of claim 3 wherein B is guanine.

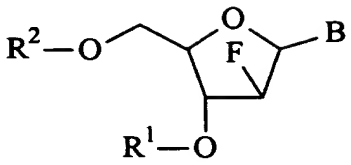
5. The compound of claim 3 wherein B is N^2-isobutyrylguanine.

6. The compound of claim 3 wherein B is adenine.

7. The compound of claim 3 wherein B is N^6-benzoyladenine.

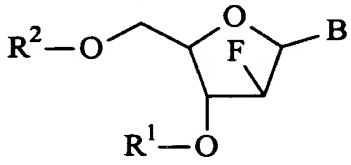
8. The compound of claim 3 wherein B is thymine.

9. The compound having the formula:



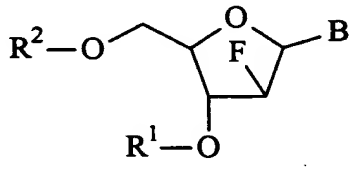
wherein B is N^2-isobutyrylguanine, R^1 and R^2 are both H.

10. The compound having the formula:



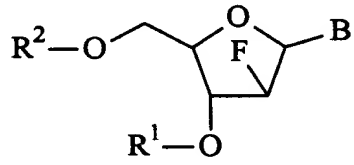
wherein B is N^4-benzoylcytosine, R^1 and R^2 are both H.

11. The compound having the formula:



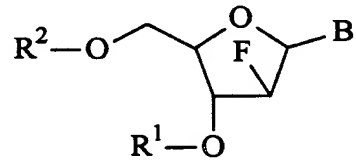
wherein B is N^6-benzoyladenine, R^1 and R^2 are both H.

12. The compound having the formula:



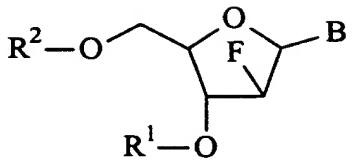
wherein B is N^2-isobutyrylguanine, R^1 is H and R^2 is 4,4'-dimethoxytrityl.

13. The compound having the formula:



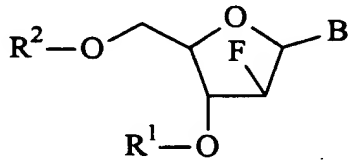
wherein B is N^4-benzoylcytosine, R^1 is H and R^2 is 4,4'-dimethoxytrityl.

14. The compound having the formula:



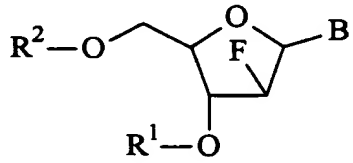
wherein B is N^6-benzoyladenine, R^1 is H and R^2 is 4,4'-dimethoxytrityl.

15. The compound having the formula:



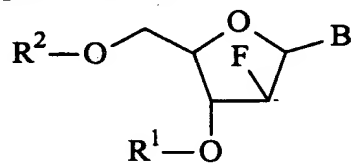
wherein B is thymine, R^1 is H and R^2 is 4,4'-dimethoxytrityl.

16. The compound having the formula:



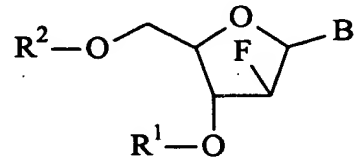
wherein B is N^2-isobutyrylguanine, R^1 is t-butyldimethylsilyl and R^2 is H.

17. The compound having the formula:



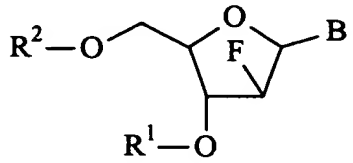
wherein B is N^4-benzoylcytosine, R^1 is t-butyldimethylsilyl and R^2 is H.

18. The compound having the formula:



wherein B is N^6-benzoyladenine, R^1 is t-butyldimethylsilyl and R^2 is H.

19. The compound having the formula:



wherein B is thymine, R^1 is t-butyldimethylsilyl and R^2 is H.

20. A modified oligonucleotide or derivative thereof comprising at least one nucleoside selected from the group consisting of an arabinonucleoside, and a 2'-deoxy-2'-fluoro-arabinonucleoside.

21. The modified oligonucleotide of claim 20 wherein said nucleoside is a 2'-arabinonucleoside .

22. The modified oligonucleotide of claim 20 wherein said nucleoside is a 2'-deoxy-2'-methylester-arabinonucleoside.

23. The modified oligonucleotide of claim 20 wherein said nucleoside is a 2'-deoxy-2'-fluoro-arabinonucleoside.

24. The modified oligonucleotide of claim 20 having a length of 2 to 30 nucleotides.

25. The modified oligonucleotide of claim 24 wherein at least one internucleoside linkage is selected from the group consisting of phosphorothioate, phosphorodithioate, morphilodate, piperazidate, methylphosphonate and phosphoroamidate.

26. The modified oligonucleotide of claim 20 wherein at least one internucleoside linkage is phosphorothioate.